A Day in the Life of a Geneticist

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As I board my metro train to go home after a seemingly heavy day, I start reflecting on the day's proceedings. It started with a message on WhatsApp- with news of the death of a baby whom I had seen a few weeks ago. The baby had come from another country, with a hope for treatment. He was brought to our Institute for a specific reason. The child had maple syrup urine disease (MSUD) and had been on dietary management. The family was looking for a one-time solution. I had guided them regarding the liver transplant, which was not an easy option, with all its difficulties and risks. Perhaps the family accepted this option as a way out and therefore went for it. Little did they know of its outcome! The baby suffered portal vein thrombosis, a known complication and could not survive (Zanetto et al., 2018).

As I opened my email, I was in for another setback. A family from Jammu had been waiting anxiously. The 12-year-old boy was diagnosed with X-linked adrenoleukodystrophy (XLALD), having presented with a history of gradual loss of vision for a few months. A typical pattern of magnetic resonance imaging (MRI) of the brain involving the posterior white matter with gadolinium enhancement had provided the diagnosis, confirmed by a subsequent abnormal very long chain fatty acid (VLCFA) analysis and genetic testing, revealing a pathogenic variant in the *ABCD1* gene. In light of recent knowledge of a 'new drug' for XLALD, Leriglitazone (https://www.minoryx.com/), we (i.e., the family and I) were very optimistic. We reached out to experts abroad and looking at the well-preserved clinical status of the child, with a calculated Loes score of <15, there was hope for approval of the drug 'on compassionate grounds'. The email, however, said otherwise - the MRI reviewed by the experts abroad revealed a Loes score well above 15, thus disallowing him for the drug. Another hope dashed to the ground.

In the course of the day, we learnt about another patient, who had received Zolgensma therapy for spinal muscular atrophy about six weeks back, struggling with severe liver dysfunction and failure. This was the sad reality after almost six months of struggle getting him to receive the magic 'gene therapy'.

As the day rolled on, another patient's consultation came up – an afternoon video consultation for a 20- month-old boy with inherited L-asparagine synthetase (ASNS) deficiency. The little boy had been diagnosed with ASNS deficiency at another hospital in South India and had reached out to us in June last year. He was optimistically started on L- asparagine therapy, after consultation with experts abroad, even though the literature evidence for its utility was scant (Sprute et al., 2019). The baby had shown improvement in the first 4 months with cessation of seizures and gain of few milestones (neck control). However, I received another blow when the parents reported a resurgence of seizures, albeit brief ones, and no further gain in milestones or weight.

Another 5-month-old patient admitted in the ward was under investigation for progressive spleno-hepatomegaly and a squint. The elevated biomarker chitotriosidase had provided a clue leading to detection of deficient beta-glucosidase activity, and a diagnosis of neuronopathic Gaucher disease. Treatment for Gaucher disease is available, however the practicality of it makes it difficult - so near yet so far. The struggle to provide enzyme replacement therapy would start now.

To end my story, another delightfully cute baby came in for a follow up. Resident of Madhya Pradesh, the now 8-month-old boy had presented at 4 months of age with a cholestatic liver disease. Upon extensive work up, including an elevated serum chitotriosidase as an extremely useful clue, the baby was finally diagnosed, via whole exome sequencing to have Niemann-Pick type C. This little baby is doing well. Though the organomegaly is

Table 1 Brief description of the genetic disorders mentioned in the article

S. No.	Name of the disorder	Etiology	Salient clinical features	Treatment options
1.	Maple syrup urine disease (MSUD)	Inborn error of branched chain amino acid catabolism, due to deficiency of the branched chain keto acid dehydrogenase (BCKDH) enzyme.	Classical presentation is with episodic encephalopathy, seizures, life threatening.	Special diet highly restricted in branched chain amino acids; management of acute crisis; liver transplantation
2.	X-linked Adrenoleukodys-trophy (ALD)	Deficiency of ABCD1 transporter in peroxisomes	Cerebral ALD - Progressive neurodegeneration; adrenal insufficiency	Supportive therapy; hematopoietic stem cell transplantation; hormonal replacement therapy; gene therapy or oral Leriglitazone (clinical trials underway)
3.	Gaucher disease	Deficiency of lysosomal beta-glucosidase enzyme	Type 1 visceral type – progressive splenohepatomegaly, hematological and bone manifestations. Type 2 and 3 – acute and chronic neuronopathic forms along with manifestations as in type 1.	Enzyme replacement therapy for type 1 and 3; substrate reduction therapy
4.	Niemann-Pick disease type C	Defect in lysosomal lipid trafficking	Progressive storage of lipids (sphingosine) with splenohepatomegaly, and progressive neurological features such as cognitive, ataxia, gaze palsy etc.	Substrate reduction therapy with Miglustat, an oral reversible inhibitor of glucosylceramide synthase
5.	Spinal muscular atrophy	Absence or reduced functioning of survivor motor neuron (SMN) protein	Primary involvement of the motor neuron, with hypotonia, involving the axial/appendicular skeleton and respiratory system. Four types, with type 1 being most severe with onset in early infancy and death by 2 years of age.	Intravenous gene therapy with onasemnogene abeparvovec (Zolgensma); intrathecal antisense oligonucleotide (ASO) therapy Nusinersen; oral exon skipping therapy Risdiplam
6.	Asparagine synthase deficiency	Deficiency of the enzyme asparagine (non-essential amino acid) synthase	Prenatal / early onset microcephaly, seizures, delayed developmental milestones	Supplementation with oral synthetic L-asparagine (limited evidence)

persistent, he is gaining milestones and feeding well, the cholestasis having subsided. This leads us to wonder about his future. Treatment with miglustat may be applicable to him in the near

future (Pineda et al., 2018), and may be available too after some efforts and with funding support through the National Policy for Rare Diseases. But, at the moment, the future remains uncertain.....

Details of the disorders and the related therapies mentioned in this article are provided in **Table 1**.

We have witnessed the changing eras – from 'only a clinical diagnosis', to the ecstasy of cytogenomic or molecular confirmation, and now, the era heralding therapies at a fast pace. Like the above cases, all families and patients come to us with hope, but are we able to do justice? The 21st century ushered promises with newer advanced therapies becoming a reality, but the struggle is still there. The struggle of availability, affordability, procurement, procedural expertise and uncertainty of long-term outcomes! Cure versus stabilization and the challenge of evolving phenotypes as patients on definitive therapy survive beyond the understood natural history of the disorder. It is the era of hope for patients and an exciting challenge for geneticists to think 'out of the box', but with a word of caution to "look before you leap" and to remember the Hippocratic oath "First do no harm".

We march on, guided by our mentors, for the sake of our patients and for the future generations of physicians, who will have learnt from our struggles and mistakes, to give their patients a bright and healthy life.

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